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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/889,430	01/17/2002	Mathieu Hubertus Maria Noteborn	2906-4992US	2965

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EXAMINER	
LI, QIAN JANICE	

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 08/26/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/889,430	NOTEBORN ET AL.	
	Examiner	Art Unit	
	Q. Janice Li	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 June 2004* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *17-38* is/are pending in the application.

4a) Of the above claim(s) *17,18,27-30 and 32* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *19-26,31 and 33-38* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *17 January 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 6/28/04 has been entered.

Claims 19, 20, 25, 36 have been amended. Claim 38 is newly added. Claims 19-26, 31, and 33-38 are under current examination.

Unless otherwise indicated, previous rejections that have been rendered moot in view of the amendment and new grounds of rejections will not be reiterated. The arguments in the response would be addressed to the extent that they apply to current rejections.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

WRITTEN DESCRIPTION

Previous rejection under this provision has been modified and appears below.

Claims 19-26, 31, and 33-38 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The methodology for determining adequacy of Written Description to convey that applicant was in possession of the claimed invention includes determining whether the application describes an actual reduction to practice, determining whether the invention is complete as evidenced by drawings, or determining whether the invention has been set forth in terms of distinguishing identifying characteristics as evidenced by other descriptions of the invention that are sufficiently detailed to show that applicant was in possession of the claimed invention (*Guidelines for Examination of Patent Applications under 35 U.S.C. § 112, p 1 "Written Description" Requirement;* Federal Register/ Vol 66. No. 4, Friday, January 5, 2001; II Methodology for Determining Adequacy of Written Description (3.)).

The claims are directed to a method for treating an inflammatory disorder or an immune disease in a subject comprising administering to the subject a gene delivery vehicle expressing an apoptin exhibiting its effect in aberrant cells involved or related to immune disease, wherein the methods requires that gene delivery vehicle has a *tropism* for targeting aberrant cells such as aberrant hematopoietic cells or fibroblast-like synoviocytes, wherein the tropism is provided with a *targeting means*, wherein preferably the means is a *viral vector* having a specific tissue/cell tropism. Given the

broadest reasonable interpretation, the practice of the claimed invention requires using a genus of starting material, preferably viral vectors having a specific tissue tropism, and thus capable of delivering the apoptin to a desired cell/tissue. Since the claims read on a therapeutic method for treating any and all inflammatory disorder or immune disease, wherein the viral vectors are administered via any route of administration, including at a site remote from the aberrant cells such as by intravenous injection reaching synoviocytes, which demands that the viral vector has a high targeting ability so that it can reach the desired aberrant cells in sufficient amount. However, the specification fails to provide an adequate disclosure for representative species of such means.

The specification prophetically teaches that in order to reduce unwanted effects of the gene delivery vehicles, it is preferred the vehicle has or is provided with a tropism for the target cells and this could be done by simply selecting a gene delivery vehicle that has a tropism such as an adenovirus (paragraph bridging pages 4 & 5). It is noted that the method encompasses targeting any cell in the body, because an inflammation/immune disease could occur in any cell type. However, the specification fails to teach the viral vectors having various cell/tissue tropisms to representative cell/tissue types or suitable for targeting aberrant cell populations. The only viral vector disclosed and illustrated as working examples in the specification is an adenoviral vector administered into a fibroblast-like synovial cell cultures. In this situation, targeting is not necessary. The disclosure of the specification and subsequent arguments presented by applicants refer to general prior art of record for the targeting means,

contemplating that recombinant adenoviruses are well known in the field of gene therapy, and need no further elaboration in the specification. Turning to the state of the art taking adenovirus as an example, it is not well known in the art that adenovirus has a tissue tropism for hematopoietic cells, even though it may be able to transfect such cells given proper transfection conditions. Although adenovirus is known for its tissue tropism to epithelial cells of respiratory system and hepatocytes, it appears that art acknowledge that such tissue tropism of the adenovirus is limited and often associated with certain routes of administration, e.g. intranasal for respiratory epithelial cells and intravenous for hepatocytes. For example, *Siders et al* (J Immunol 1998;160:5465-74) clearly teach they use i.v. route for adv-IL-12 "BECAUSE THE LIVER IS A PRIMARY SITE OF INFECTION AFTER I.V.-ADMINISTERED ADENVIRUS" (abstract). Gregory et al (US 6,093,567) teach "ADENOVIRUS HAS A NATURAL TROPISM FOR AIRWAY EPITHELIA. THEREFORE, ADENOVIRUS-BASED VECTORS ARE PARTICULARLY PREFERRED FRO RESPIRATORY GENE THERAPY APPLICATIONS" (Column 4, lines 17-20). *Worth et al* (Clin Cancer Res. 2000;6:3713-8) teach that administration of Adv-IL-12 intranasally found no expression in the liver (left column, page 3715). A closer look of the print publications, at the time before and up to the point long after the instant effective filing date, would find that successful gene therapy of arthritis often achieved by intraarticular administration where adenovirus infects synovial cells efficiently (e.g. Zhang et al, J Clin Invest 1997;100:1951-7; and Goossens et al, Clin Exp Rheumatol 2002;20:415-9). This evidenced that adenoviral vector does have the ability to infect synovial cells, but such ability differs from tissue tropism. There is no-known and specific tissue tropism that would allow the adenovirus to target specifically to synovial

cells by an administration remote from the site of synovial cells, and the specification fails to teach otherwise. In fact, the only working example provided by the specification is administering adenovirus to the culture of fibroblast-like synovial cells, which apparently does not require targeting. As to viruses that could specifically target other aberrant cells associated with inflammation or an autoimmune disease, for example, the hematopoietic cells or thyroidal cells, the specification fails to shed any light with regard to what type of virus would have such specific tissue tropism. Considering the numbers of numerous cell types that may associated with an autoimmune/inflammatory disorder, and the degree of affinity required, the specification fails to provide an adequate written description for the representative species of viral vectors having a specific tissue tropism for targeting. The Revised Interim Guidelines for "Written Description" requirement states: "THE CLAIMED INVENTION AS A WHOLE MAY NOT BE ADEQUATELY DESCRIBED IF THE CLAIMS REQUIRE AN ESSENTIAL OR CRITICAL ELEMENT WHICH IS NOT ADEQUATELY DESCRIBED IN THE SPECIFICATION AND WHICH IS NOT CONVENTIONAL IN THE ART" (Column 3, page 71434),

In the response filed, applicants ignores the teaching of the cited art of record and insists on that targeting means is well known in the art and thus not required to be in the specification, and citing *In re Gay* case law as support. However, as an initial matter, it is noted that the arguments of counsel cannot take the place of evidence in the record. *In re Schulze*, 346 F.2d 600, 602, 145 USPQ 716, 718 (CCPA 1965). Further, an adequate written description for means of tissue tropism having a specific targeting ability requires more than a mere statement that it is part of the invention; what is required is a description of the means itself. It is not sufficient to define the means

solely by its principal biological property, i.e. "**has a tissue tropism for hematopoietic cells**" or "**has a tissue tropism for fibroblast-like synoviocytes**", because disclosure of no more than that, as in the instant case, is simply a wish to know the identity of any gene delivery vehicle with that biological property. Also, naming a type of material generically known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material. Thus, claiming all vehicles that achieve a result without defining what means will do is not in compliance with the description requirement. Rather, it is an attempt to preempt the future before it has arrived. (See *Fiers v. Revel*, 25 USPQ2d 1601 (CA FC 1993) and *Regents of the Univ. Calif. v. Eli Lilly & Co.*, 43 USPQ2d 1398 (CA FC, 1997)). With respect to the method claims, adequate description of the methods first requires an adequate description of the materials, i.e. specific chemical structure and physical properties of the material, which provide the means for practicing the invention. The court has made it very clear "CONCEPTION OF CHEMICAL COMPOUND REQUIRES THAT INVENTOR BE ABLE TO DEFINE COMPOUND SO AS TO DISTINGUISH IT FROM OTHER MATERIALS, AND TO DESCRIBE HOW TO OBTAIN IT, RATHER THAN SIMPLY DEFINING IT SOLELY BY ITS PRINCIPAL BIOLOGICAL ACTIVITY". *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016 (Fed. Cir. 1991). In the instant case, the specification only names the material (a gene delivery vehicle having a tropism for target cells) but fails to define the means so as to allow the skilled in the art to identify the material, and thus fails to provide an adequate description for the genus of the gene delivery vehicles having a tropism for a specific target cell, and it fails to provide an adequate description for the genus of targeting means to any cell associated with any

immune or inflammatory disorders, and accordingly does not provide a reasonable guide for those seeking to practice the invention.

Claims 19 and 20 recite "a gene capable of expressing" apoptin protein. The term "gene" refers not only to a coding sequence but also to an entire genomic structure (including introns and all regulatory regions upstream and downstream of coding sequences), and since the entire genomic structure of a representative number of eukaryotic apoptin genes is not known, the specification fails to provide an adequate written description for what is now claimed.

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481, 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

In view of these considerations, a skilled artisan would not have viewed the teachings of the specification as sufficient to show that the applicant was in possession of the claimed invention commensurate to its scope because it does not provide adequate written description for the broad classes of *gene delivering vehicle having a tropism for an aberrant cell*". Therefore, the specification fails to meet the written description provision of 35 U.S.C. §112, first paragraph.

Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

To the extent that the claimed invention is not adequately described in the instant disclosure, claims 19-26, 31, and 33-38 are also rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention, since a disclosure cannot teach one to make or use something that has not been adequately described that is not conventional in the art, and since without such targeting means, the gene delivery vehicle could not sufficiently reach the target cells if administered from a remote site.

In the response filed, applicants insists on that such knowledge is well known in the art and thus not required to be in the specification, and citing In re Gay case law as support. However, it is noted that the Federal Circuit has stated that:

> a specification need not disclose what is well known in the art. See, e.g., Hybritech Inc. v. Monoclonal Antibodies, Inc., 802 F.2d 1367, 1385, 231 USPQ 81, 94 (Fed. Cir. 1986). However, that general, oft-repeated statement is merely a rule of supplementation, not a substitute for a basic enabling disclosure. It means that the omission of minor details does not cause a specification to fail to meet the enablement requirement. However, **when there is no disclosure** of **any specific starting material or of any of the conditions under which a process can be carried out, undue experimentation is required; there is a failure to meet the enablement requirement that cannot be rectified by asserting that all the disclosure related to the process is within the skill of the art**. It is the specification, not the knowledge of one skilled in the art, that must supply the novel aspects of an invention in order to constitute adequate enablement.

Genentech Inc. v. Novo Nordisk A/S, 42 USPQ2d 1005 (CAFC 1997) (emphasis added).

The rule that a specification need not disclose that which is well known in the art simply means that omission of minor details does not cause a specification to fail the enablement requirement, and is not a substitute for an enabling disclosure. However, if there is no disclosure of starting materials and of conditions under which the process

can be carried out, undue experimentation is required. Failure to provide such teachings cannot be rectified by asserting that the disclosure of the missing necessary information was well known in the prior art. See *Genentech Inc. v. Novo Nordisk A/S*, 42 USPQ2d 1001, 1005 (CA FC, 1997).

One cannot extrapolate the teachings of the specification to the scope of the claims because the skilled artisan cannot envision the detailed structures of gene delivery vehicle having a specific targeting means encompassed by these claims, thus, one would not know how to use the invention without first carrying out undue experimentation to determine what is the proper target for a specific tissue tropism, how to provide such. Therefore, in view of the limited guidance, the lack of predictability of the art, and the breadth of the claims, one skill in the art could not practice the invention without undue experimentation.

Claims 19-26, 31, and 33-38 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treating rheumatoid arthritis in a subject comprising *intraarticular* administering a recombinant adenovirus encoding and expressing an apoptin, does not reasonably provide enablement for treating any inflammatory disorder, any immune disease comprising administering an gene delivery vehicle via any route of administration. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The factors to be considered when determining whether the disclosure satisfies the enablement requirements and whether undue experimentation would be required to make and use the claimed invention are summarized in *In re Wands*, (858 F2d 731, 737, 8 USPQ 2d 1400, 1404, (Fed Cir.1988)). These factors include but are not limited to the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability of the art, the breadth of the claims, and amount of direction provided. The factors most relevant to this rejection are the scope of the claims relative to the state of the art and the levels of the skilled in the art, and whether sufficient amount of direction or guidance are provided in the specification to enable one of skill in the art to practice the claimed invention.

Given the broadest reasonable interpretation, the claims encompass treating any inflammatory disorder, any immune disease comprising administering any gene delivery vehicle via any route of administration. However, the only type of inflammatory disease contemplated in the specification is arthritis particularly the RA. The specification teaches that apoptin will induce apoptosis in synoviocytes from arthritis patient but not normal synovial cells. However, the specification fails to teach whether apoptin would induce apoptosis in other aberrant cell types beyond synoviocytes, and which cell population to target and how to target for any other of numerous diseases encompassed by the claims. Since it is known that apoptin would only induce apoptosis in tumor cells or transformed tumor cell lines but not normal cell types (Oorschot et al, PNAS 1997;94:5843-7 and Adv Exp Med Biol 1999;457:245-9, abstract), one can not

extrapolate from arthritic synoviocytes to any type of aberrant cells associated with an immune disorder.

Even assuming *arguendo* that apoptin could induce any aberrant cells associated with an inflammation to undergo apoptosis, in view of the state of the art in immune diseases in general and autoimmunity in particular, the nature and variety of the diseases is so complex, the initiation, pathogenesis, and mechanism of sustaining are still not fully understood. It is unknown and the specification fails to teach whether administering a nucleic acid encoding apoptin could achieve the goal of treating an immune disease, particularly an autoimmune disease. For example, in systemic lupus erythematosus (SLE), the aberrant cells exist ubiquitously and abundant, which viral vector have the tropism to target these aberrant cells? In type I diabetes, pancreatic islet cells became the target of cytotoxic T cells and aberrant, would deliver apoptin to pancreas ameliorate diabetes or just bring islet cells to death? Sometimes, the target of an autoimmune disease is a normal cellular receptor, such as AchR for myathesnia gravis, and GpIIb:IIIa fibrinogen receptor for autoimmune thrombocytopenic purpura, then the consequence of apoptin effects on the aberrant cells is unpredictable if not undesirable. These are some of the examples why the gene therapy art is still under development. Although the specification outlines the principle of the invention, it fails to teach beyond the arthritis, how to treat the broadly encompassed diseases. *Kalden et al* (Advances in Immunology 1998, 68; pages 333-395, paragraph 2 through page 396 paragraph 4) teach, "EVEN RELATIVELY "SIMPLE" EXPERIMENTAL MODELS OF AUTOIMMUNITY REMAIN DIFFICULT TO TREAT", AND "THE EXPERIMENTAL MODELS OF AUTOIMMUNE DISEASES ARE

CLEARLY DISTINCT DISORDERS OF HIGHLY STRUCTURED AUTOIMMUNITY; DESPITE THE FACT THAT THEY SHARE SOME IMMUNOPATHOGENETIC PATHWAYS, THEY RELY ON QUITE DIFFERENT POLYGENETIC BACKGROUNDS. THUS, THE BENEFICIAL EFFECTS OF A CERTAIN TREATMENT IN ONE MODEL CANNOT NECESSARILY BE EXTRAPOLATED TO ANOTHER". Apparently, it is yet to be routine in the art for treating inflammatory and immune disorder by any means, particularly by gene therapy. Accordingly in view of the state of the art and the guidance provided in the specification, it would require undue experimentation for the skilled artisan intending to practice the invention to figure out for themselves how to practice the claimed invention.

The claimed invention requires gene targeting in vivo to aberrant cells associated with an immune disease. While progress has been made in recent years for gene transfer *in vivo*, vector targeting to desired cells *in vivo* continues to be unpredictable and inefficient as supported by numerous teachings available in the art. For example, *Deonarain* (1998, Expert Opin. Ther. Pat., Vol. 8, pages 53-69) indicate that one of the biggest problems hampering successful gene therapy is the "ability to target a gene to a significant population of cells and express it at adequate levels for a long enough period of time" (page 53, first paragraph). Deonarain reference gives high hope to targeted gene delivery, but the discussed strategies are still under investigation, and at the time, they were much less efficient than viral gene delivery (Conclusion). *Deonarain* teaches, "GENE DELIVERY REMAINS THE MAJOR TECHNOLOGICAL STUMBLING BLOCK IN GENE THERAPY STRATEGIES", (2nd paragraph, page 54).

Miller et al (1995, FASEB J., Vol. 9, pages 190-199), acknowledge various vector system available in the art, then teach, "NO SINGLE DELIVERY SYSTEM IS LIKELY TO BE

UNIVERSALLY APPROPRIATE, FOR INSTANCE, THE REQUIREMENTS OF GENE THERAPY FOR CYSTIC FIBROSIS ARE GREATLY DIFFERENT FROM THOSE OF CANCER" (1st paragraph, page 190). "ONCE AGAIN, TARGETING AT THE LEVEL OF THE VECTOR HAS NOT YET BEEN PARTICULARLY WELL DEVELOPED; HENCE, LIPOSOME OR VIRAL-MEDIATED DELIVERY OF THE CFTR BEEN TO AIRWAY EPITHELIAL CELLS OF CF PATIENTS HAS RELIED LARGELY ON THE LOCALIZED DELIVERY OF THE VECTORS DIRECTLY TO THE AFFECTED TISSUES" (1st paragraph, page 198)

The claimed invention calls for use of viral vectors, while each type of virus has different tissue tropism and different efficiency in transducing different types of cells. *Robbins et al* (Pharmcol Ther 1998;80:35-47) teach that each type of vector system has its unique advantages and limitations, "RETROVIAL VECTORS CAN PERMANENTLY INTEGRATE INTO THE GENOME OF THE INFECTED CELL, BUT REQUIRE MITOTIC CELL DIVISION FOR TRANSDUCTION. ADENOVIRAL VECTORS CAN EFFICIENTLY DELIVER GENES TO A WIDE VARIETY OF DIVIDING AND NONDIVIDING CELL TYPES, BUT IMMUNE ELIMINATION OF INFECTED CELLS OFTEN LIMITS GENE EXPRESSION IN VIVO. HERPES SIMPLEX VIRUS CAN DELIVER LARGE AMOUNTS OF EXOGENOUS DNA; HOWEVER, CYTOTOXICITY AND MAINTENANCE OF TRANSGENE EXPRESSION REMAIN AS OBSTACLES. AAV ALSO INFECTS MANY NONDIVIDING AND DIVIDING CELL TYPES, BUT HAS LIMITED DNA CAPACITY" (abstract). For *in vivo* gene therapy in a patient with an immune disease, these are the factors have to be considered. *Verma et al* (Nature 1997;389;239-42) teach "THE USE OF VIRUSES IS A POWERFUL TECHNIQUE, BECAUSE MANY OF THEM HAVE EVOLVED A SPECIFIC MACHINERY TO DELIVER DNA TO CELLS. HOWEVER, HUMANS HAVE AN IMMUNE SYSTEM TO FIGHT OFF THE VIRUS, AND OUR ATTEMPTS TO DELIVER GENES IN VIRAL VECTORS HAVE BEEN CONFRONTED BY THESE HOST RESPONSE" (last paragraph of left column on page 239). Verma et al teaches particularly regarding to retroviral vector, "A CRITICAL LIMITATION OF RETROVIRAL VECTORS IS

THEIR INABILITY TO INFECT NON-DIVIDING CELLS". (paragraph bridging left and middle columns of page 240), while the aberrant cells are most likely non-dividing cells. Moreover, vectors, whether delivered systemically or locally in vivo have unpredictable efficacy in infecting/transfecting the target cells/tissue and that it is further unpredictable whether the transfected cells will express a therapeutic level of the heterologous gene. The specification fails to teach how to overcome the aforementioned difficulties in the art. It would have required undue experimentation for the skilled artisan intending to practice the instant invention.

While, the intent for citing the references is not to say that gene therapy has not or can never be achieved, the intent is to provide art taught reasoning as to why the instant claims are not fully enabled, and to illustrate the general state of the art in gene therapy to properly determine whether additional and specific guidance should be provided by the specification. As indicated by *French Anderson,* who (Hum Gene Ther 2002;13:1261-2) compared the reality in practicing gene therapy with the launching of space shuttle. "THERE ARE HUNDREDS OF CRITICAL STEPS, ALL OF WHICH MUST WORK SMOOTHLY AND EFFICIENTLY FOR THE WHOLE MISSION TO BE SUCCESSFUL...EVERY SYSTEM MUST BE HIGHLY SOPHISTICATED IN ORDER TO ENSURE SUCCESS. SO, TOO, WITH THE GENE THERAPY" (Section 1, page 1261), who asked at the time long after instant filing date, "WHY HAS IT BEEN SO HARD TO OBTAIN SUCCESS IN GENE THERAPY CLINICAL TRIALS", and who predicted that 2005 may see the first licensed gene therapy product. These teachings establish that the nature of the transgene, the vector construct used, the means of delivery, and models and criteria for

evaluation are all contributing to the novel aspects of gene therapy, and these elements were not yet routine for gene therapy at the time of instant filing date.

Accordingly, in view of the quantity of experimentation necessary to determine the parameters for inducing apoptosis in selected aberrant cells *in vivo* at therapeutic levels, in particular for the treatment of any and all inflammatory/immune diseases, the lack of direction or guidance provided by the specification as well as the absence of working examples with regard to *in vivo* gene therapy of any disease, and the breadth of the claims directed to the use of numerous therapeutic gene delivery vector equipped with a specific tissue tropism, it would have required undue experimentation for one skilled in the art to make and/or use the claimed invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 37 and 38 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 37 is vague and indefinite because the claimed process comprises a step of "infecting" the fibroblast-like synoviocyte. The specification fails to define the term, it is unclear in the context of the claim what type of action the term encompasses and excludes, and thus the metes and bounds of the claims are uncertain.

Claim 38 is vague and indefinite because the claimed process comprises a step of "targeting" the recombinant adenovirus to a fibroblast-like synoviocyte. The

specification fails to define the term, it is unclear in the context of the claim what type of action the term encompasses and excludes, and thus the metes and bounds of the claims are uncertain.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (f) he did not himself invent the subject matter sought to be patented.

Claims 19 and 20 stand rejected under 35 U.S.C. 102(f) because the applicant did not invent the claimed subject matter. The subject matter as claimed encompasses that of claims 27 and 28 of U.S. patent application 09/733,416; and that claims 15-17 of U.S. patent application 09/764,176. These applications have a different inventive entity.

Please note that previous rejection under this provision over claims 27 and 28 of U.S. patent application 09/733,416 has been reinstated because the rejected claims are still pending.

Applicants argue that the cited application has a common inventor with the present application. Applicants are reminded that since the cited application lists different inventors compared to the present application, it considered as different inventive entity. The rejection could be overcome by an affidavit under 37 CFR 1.131, or an affidavit under 37 CFR 1.132 as indicated in MPEP 2137.

WHILE DERIVATION WILL BAR THE ISSUANCE OF A PATENT TO THE DERIVER, A DISCLOSURE BY THE DERIVER, ABSENT A BAR UNDER 35 U.S.C. 102(B), WILL NOT BAR THE ISSUANCE OF A PATENT TO THE PARTY FROM WHICH THE SUBJECT MATTER WAS DERIVED. IN RE COSTELLO, 717 F.2D 1346,

1349, 219 USPQ 389, 390-91 (FED. CIR. 1983) ("[A] PRIOR ART REFERENCE THAT IS NOT A STATUTORY BAR MAY BE OVERCOME BY TWO GENERALLY RECOGNIZED METHODS": AN AFFIDAVIT UNDER 37 CFR 1.131, OR AN AFFIDAVIT UNDER 37 CFR 1.132 "SHOWING THAT THE RELEVANT DISCLOSURE IS A DESCRIPTION OF THE APPLICANT'S OWN WORK"); IN RE FACIUS, 408 F.2D 1396, 1407, 161 USPQ 294, 302 (CCPA 1969) (SUBJECT MATTER INCORPORATED INTO A PATENT THAT WAS BROUGHT TO THE ATTENTION OF THE PATENTEE BY APPLICANT, AND HENCE DERIVED BY THE PATENTEE FROM THE APPLICANT, IS AVAILABLE FOR USE AGAINST APPLICANT UNLESS APPLICANT HAD ACTUALLY INVENTED THE SUBJECT MATTER PLACED IN THE PATENT) (MPEP 2137)

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The prior rejection of Claims 19, 20, and 26 under 35 U.S.C. 103(a) as being unpatentable over *Sata et al* (PNAS 1998 Feb;95:1213-7), in view of *Zuckermann et al* (US 6,468,986), is withdrawn in view of the argument that it is not known at the time of filing, that synoviocytes of rheumatoid arthritis could be induced to undergo apoptosis by the apoptin. Such fact is further evidenced by the teachings of Oorschot et al (PNAS 1997;94:5843-7 and Adv Exp Med Biol 1999;457:245-9, abstract).

The prior rejection of Claim 37 under 35 U.S.C. 103(a) as being unpatentable over *Sata et al* (PNAS 1998 Feb;95:1213-7) and *Zuckermann et al* (US 6,468,986) as applied to claims 19, 20, 26 above, and further in view of *Ledley et al* (US 5,792,751), is withdrawn in view of the argument that it is not known at the time of filing, that synoviocytes of rheumatoid arthritis could be induced to undergo apoptosis by the

apoptin. Such fact is further evidenced by the teachings of Oorschot et al (PNAS 1997;94:5843-7 and Adv Exp Med Biol 1999;457:245-9, abstract).

The prior rejection of Claims 19-22, 26, 36 under 35 U.S.C. 103(a) as being unpatentable over *Sata et al* (PNAS 1998 Feb;95:1213-7) and *Zuckermann et al* (US 6,468,986) as applied to claims 19, 20, 26 above, and further in view of *McCormick et al* (US 5,801,029), and *Bujard et al* (US 5,814,618), is withdrawn in view of the argument that it is not known at the time of filing, that synoviocytes of rheumatoid arthritis could be induced to undergo apoptosis by the apoptin. Such fact is further evidenced by the teachings of Oorschot et al (PNAS 1997;94:5843-7 and Adv Exp Med Biol 1999;457:245-9, abstract).

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 19 and 20 stand provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 22 and 25 of copending Application No. 09/403,213, for reasons of record and because the amended claims 22 and 25 of the cited application are drawn to delivery the nucleic acid of VP3, which is an alternate name for apoptin.

Applicants indicate that if any issues remain, upon an indication of allowable subject matter, the issue will be addressed then.

Until the issue is addressed, the rejection stands for reasons of record and foregoing.

Claims 19 and 20 stand rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 15-17 of copending Application No. 09/764,176, now allowed. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of the present application and that of the cited patent application are each drawn to a method comprising administering to a subject a gene delivery vehicle expressing an apoptosis inducing agent exhibiting its effect in aberrant cells, wherein the agent is apoptin or derivative.

Applicants indicate that if any issues remain, upon an indication of allowable subject matter, the issue will be dealt with then.

In response, until the issue is dealt with, the rejection stands for reasons of record and foregoing.

The prior provisional rejection of claims 19 and 20 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 27 and 28 of copending Application No. 09/733,416 is reinstated for reasons of record because claims 27 and 28 remain pending.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Q. Janice Li** whose telephone number is 571-272-0730. The examiner can normally be reached on 9:30 am - 7 p.m., Monday through Friday, except every other Wednesday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Amy Nelson** can be reached on 571-272-0804. The fax numbers for the organization where this application or proceeding is assigned are **703-872-9306**.

Any inquiry of formal matters can be directed to the patent analyst, **Dianiece Jacobs**, whose telephone number is (571) 272-0532.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance.

Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

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QJL
August 18, 2004